REMARKS

The amendments and remarks shown in this response were initially filed on July 18, 2005 in response to a Final Office Action mailed on April 18, 2005. The Examiner replied in an Advisory Action, mailed on August 22, 2005, that the above-detailed amendments to the claims added a new limitation, namely "protein-protein interactions" that had not been previously considered on the merits and thus would require new search and consideration. Thus, because this response was filed after a Final Office Action was mailed, the amendment was not entered and the Examiner considered the remarks of the previous response moot. Applicants herein refile this response with a Request for Continued Examination, filed herewith.

Claims 1-3 and 5-9 are currently pending and under examination in the application. Claims 11 and 12 were previously withdrawn as being directed to non-elected subject matter.

Claims 1 and 5 have been amended solely to expedite patent prosecution in accordance with the U.S. Patent Office Business Goals (65 Fed. Reg. 54604 (September 8, 2000)). Applicant reserves the right to present any cancelled subject matter in a co-pending application.

Amended claims 1 and 5 recite "protein-protein interaction" and "where the plurality of proteins are screened concurrently" (see, *inter alia*, page 1, lines 12-15; page 4, lines 10-12; page 7, lines 9-12; page 9, lines 9-22 to page 10, lines 6-22; page 16, lines 3-10; page 18, lines 10-16; page 19, lines 1-20 to page 20, lines 1-8; and Example I, page 22, lines 1-19; and Examples II-IV, page 23, lines 3-22 of the application as originally filed).

Newly added claim 13 recites "[a] method of correlating proteomic interaction(s) with oxygen tension comprising (a) screening for protein levels of a plurality of proteins, where the screening is performed in room air, and where the plurality of proteins are screened concurrently; (b) screening for protein levels of a plurality of proteins, where the screening is performed in the presence of decreased oxygen tension, and where the plurality of proteins are screened concurrently; and (c) correlating the protein level(s) with oxygen tension by identifying at least one different protein level between (a) and (b)" (see, *inter alia*, page 7, lines 6-12; and Example IV, page 23, lines 18-22 of the originally filed application)..

Newly added claim 14 recites "[t]he method of Claim 13 where at least one protein employed in the determination is associated with a physiological process or a pathophysiological process" (see, *inter alia*, page 7, lines 6-12 of the application as originally filed).

Newly added claim 15 recites "[t]he method of Claim 13 where a plurality of determinations are made in step (b) with different oxygen tensions being employed in each determination" (see, *inter alia*, page 20, lines 1-3 of the application as originally filed).

Newly added claim 16 recites "[t]he method of Claim 15 where the oxygen tensions employed are in step (b) range from 0.1 mm Hg to 145 mm Hg" (see, *inter alia*, page 19, lines 19-20 of the application as originally filed).

Newly added claim 17 recites "[t]he method of Claim 13 where the different protein levels in step (c) are used to identify protein functions associated with a pathophysiological process" (see, *inter alia*, page 20, lines 6-8 of the application as originally filed).

These amendments are supported by the application as originally filed, and do not constitute new matter. Specific support for the amendments is shown in parentheses, above. Entry of these amendments in the application is respectfully requested.

Previous Rejections

The Examiner has withdrawn all previous rejections from the Office Action mailed July 13, 2004 (Office Action, page 2).

35 U.S.C. §112, First Paragraph

Claims 1-3 and 5-9 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (Office Action, page 3). The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor has possession of the claimed invention at the time the application was filed. *Id.* The Examiner states that the phrase "a proteomic interaction between at least one protein and a plurality of proteins" includes new matter. *Id.*

Applicant respectfully disagrees.

The application specifically teaches that proteomic interactions (e.g., protein-protein interactions, protein-DNA interactions, protein activity, and protein expression levels) can be screened by several well-known means (see, *inter alia*, page 9, lines 3-22 to page 11, lines 1-8 of the originally filed application). However, solely for the purpose of expediting patent prosecution, claims 1 and 5 have been amended and claim 13 has been added as follows.

1. A method of establishing a protein-protein interaction map comprising
(a) screening for a protein-protein interaction between at least one protein and a plurality of proteins, where the screening is performed in the absence of a simulated redox state perturbation, and where the plurality of proteins are screened concurrently;
(b) screening for a protein-protein interaction between the at least one protein and a plurality of proteins, where the screening is performed in the presence of a simulated redox perturbation, and where the plurality of proteins are screened concurrently; and
(c) generating the protein-protein interaction map by identifying at least one different protein-protein interaction between (a) and (b).

5. A method of correlating protein-protein interaction(s) with oxygen tension comprising
(a) screening for a protein-protein interaction between at least one protein and a plurality of proteins, where the screening is performed in room air, and where the plurality of proteins are screened concurrently;
(b) screening for a protein-protein interaction between the at least one protein and a plurality of proteins, where the screening is performed in the presence of decreased oxygen tension, and where the plurality of proteins are screened concurrently; and
(c) correlating the protein-protein interaction(s) with oxygen tension by identifying at least one different protein-protein interaction between (a) and (b).

13. A method of correlating protein levels(s) with oxygen tension comprising
(a) screening for protein levels of a plurality of proteins, where the screening is performed in room air, and where the plurality of proteins are screened concurrently;
(b) screening for protein levels of a plurality of proteins, where the screening is performed in the presence of decreased oxygen tension, and where the plurality of proteins are screened concurrently; and

(c) correlating the protein level(s) with oxygen tension by identifying at least one different protein level between (a) and (b).

The Examiner states that the instant specification provides support only for protein-protein interactions measured by two-hybrid systems (Office Action, page 4). Yet, the application specifically teaches that protein-protein interactions and protein levels can be screened by several well-established techniques, including those published by:

- Fung et al., 2001 (protein chips, microfluidic protein chips, peptide arrays, surface plasmon resonance (SPR), surface-enhanced laser desorption/ionization (SELDI), and time of flight-mass spectroscopy (TOF-MS); Exhibit 1, see page 65, right column to page 66, left column; and page 67, left column),

- Delneri et al., 2001 (two-dimensional gel electrophoresis, multidimensional protein identification technique (MudPIT), matrix-assisted laser desorption/ionization mass spectroscopy (MALDI-MS), and isotope-coded affinity tagging (ICAT); Exhibit 2, see page 88, right column to page 89, left column),

- Zhu et al., 2001 (proteome chips; Exhibit 3, see page 2101, right column to page 2102, left and center columns), and

- Sakurai et al., 1998 (orphan receptor cell lines; Exhibit 4, see page 573, right column, bottom) (see, *inter alia*, page 9, lines 3-22 to page 11, lines 1-8 of the originally filed application).

For the Written Description requirement, it is noted that Applicant need not disclose in detail those aspects of the invention which are well known to persons of ordinary skill in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, and 1384 (Fed. Cir. 1986); MPEP § 2163. This is particularly true for mature technologies, where publications and patents are available to skilled artisans. *See In re Hayes Microcomputer Products, Inc.*, 982 F.2d 1527, 1534-35 (Fed. Cir. 1992); MPEP §2163; *see*, also, Exhibits 1-4.

Moreover, it is not necessary for the application to describe *exactly* the claimed subject matter, but only to convey with *reasonably clarity* that Applicant was in possession thereof. *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000). Here, Applicant's claims encompass methods of screening protein-protein interactions and protein levels and the instant application describes numerous well known and widely published approaches for performing such screens.

For at least the reasons set forth above, claims 1-3 and 5-9 presented herein, as well as newly added claims 13-17, are supported by the application as originally filed. Reconsideration is respectfully requested.

35 U.S.C. §102(b)

Claims 1-3 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Cominacini et al., 1997, *Free Radical Biology & Medicine*, 22:117-127 ("Cominacini"; Office Action, page 4). According to the Office Action, Cominacini reports the expression levels of ICAM-1, VCAM-1, and E-selectin in the presence and absence of oxidized LDL protein (Office Action, page 5).

Applicant respectfully traverses.

Anticipation under 35 U.S.C. §102 requires that the cited reference teach every aspect of the claimed invention. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §706.02 IV. Thus, "[t]he identical invention must be shown in as complete detail as contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); MPEP §2131.

Here, the claimed methods include i) screening for a protein-protein interaction between at least one protein and a plurality of proteins; ii) screening for protein-protein interaction(s) in room air and reduced oxygen tension; or iii) screening for protein levels of a plurality of proteins in room air and in reduced oxygen tension, none of which are taught or suggested by Cominacini.

For at least these reasons, Cominacini cannot anticipate the subject matter of claims 1-3 or 5-9 presented herein, or newly added claims 13-17. Reconsideration is respectfully requested.

35 U.S.C. §103(a)

Claims 1-3 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable in view of Nishiyama et al., 1999, *J. Biol. Chem.*, 274:21645-50 ("Nishiyama"; Office Action, page 6). According to the Office Action, Nishiyama reports the binding interaction between TRX and TBP-2 in the presence of redox modifiers. *Id.* The Examiner states that it would have been obvious to one of skill in the art to characterize the binding interaction of TRX with other candidates. *Id.* The Examiner states that this characterization would merely involve the duplication of steps used for TRX and TBP. *Id.*

Applicant respectfully traverses.

As amended, claim 1 reads:

> 1. A method of establishing a protein-protein interaction map comprising
> (a) screening for a protein-protein interaction between at least *one protein and a plurality of proteins*, where the screening is performed in the absence of a simulated redox state perturbation, and *where the plurality of proteins are screened concurrently*;
> (b) screening for a protein-protein interaction between the at least *one protein and a plurality of proteins*, where the screening is performed in the presence of a simulated redox perturbation, and *where the plurality of proteins are screened concurrently*; and
> (c) generating the protein-protein interaction map by identifying at least one different protein-protein interaction between (a) and (b). (Emphasis added).

For analysis under 35 U.S.C. §103, it is essential to consider all of the elements of the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F.2d 1524, 1530 (Fed. Cir. 1984); MPEP §2141.02. Each express claim limitation must be taken into account. *See, e.g., Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447-49 (Fed. Cir. 1986); MPEP §2141.02.

Here, Applicant claims encompass a method of screening for a protein-protein interaction between at least *one protein and a plurality of proteins*, where the screening is performed in the *presence and absence of a simulated redox state perturbation* and *where the plurality of proteins are screened concurrently.*

Yet, Nishiyama does not teach or suggest at least these elements in the pending claims. Nishiyama reports only the interaction of *one* protein (TRX) with one other protein (TBP-2) (see, e.g., Figure 3). Nishiyama does not teach or suggest the screening of at least one protein and a plurality of proteins. Nor does Nishiyama teach or suggest the concurrent screening of the plurality of proteins. As such, Nishiyama cannot make obvious the subject matter of the present claims.

According to the Office Action, Nishiyama shows that the interaction between TRX and TBP-2 is inhibited by the presence of certain redox reagents (Office Action, page 6). However, Nishiyama reports that TRX was treated with "reducing/oxidizing reagents for 15 min at room temperature and then *washed [five times] with degassed...buffer* and subjected to a binding assay..." (Nishiyama, see page 21646, right column, and Figure 3).

Thus, the reducing/oxidizing reagents are *removed* by Nishiyama by several rounds of washing that precede the binding assay. In contrast, Applicant teaches and claims screens where the screening is performed in the *presence and absence of a simulated redox state perturbation* (see above). Because Nishiyama does not teach or suggest at least these elements in the pending claims, it cannot make obvious the subject matter of these claims.

Moreover, although a claimed invention is alleged to be within the capabilities of one of ordinary skill in the art, this is not sufficient by itself to establish obviousness. MPEP §2143.01; *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Even where a prior art reference may be capable of being modified as claimed, there must be a suggestion or motivation in the reference to do so in order to establish obviousness. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990); MPEP §2143.01.

Here, there is no suggestion or motivation to modify Nishiyama to produce method of screening for a protein-protein interaction between at least *one protein and a plurality of proteins* and *where the plurality of proteins are screened concurrently*. Even assuming *arguendo* that the steps of Nishiyama could be duplicated for other TRX binding candidates (which Applicant contests), this would involve the process of:

i) Cloning the binding candidate from the cDNA library; ii) Subcloning the coding region from the binding candidate into a TNT expression vector; iii) Preparing and isolating the TRX-GST fusion protein; iv) Treating the TRX-GST fusion protein with DTT, diamide, or hydrogen peroxide; v) Preparing and isolating *in vitro* translated, ^{35}S-labeled binding candidate; vi) Washing the TRX-GST fusion protein; vii) Incubating the TRX-GST fusion protein with the ^{35}S-labeled binding candidate; and vii) Analyzing the binding by SDS-PAGE analysis and autoradiography.

As such, Nishiyama is not amenable to concurrent (e.g., high throughput) screening and the "mere duplication" of steps in Nishiyama cannot be used to obtain the claimed invention.

Applicant notes that the motivation to modify references under 35 U.S.C. §103 must come from the prior art, itself. *In re Mills*, 916 F.2d at 682. Thus, it is essential:

> "to forget what...has been taught about the claimed invention and cast the mind back to the time the invention was made to occupy the mind of one skilled in the art who is presented only with the references and...the then-accepted wisdom in the art." *In re Fine*, 837 F.2d at 1075 (citing *W.L. Gore*, 721 F.2d at 1553); MPEP §2141.01.

It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the cited references so that the claimed invention is alleged to be obvious. *In re Fritch*, 972 F.2d at 1266.

In the instant case, Nishiyama does not teach or suggest all of the elements in the pending claims and there is no independent suggestion or motivation to modify or combine the reports of Nishiyama to obtain the claimed invention. For at least these reasons, pending claims 1-3 cannot

be considered unpatentable over Nishiyama and a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is respectfully requested.

CONCLUSION

A favorable action on the merits is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance.

Applicant believes no further fee is due at this time; however, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311, Reference No. 24862-503, Customer No. 30623.

Respectfully submitted,

Dian M. Coughlin Reg. No. 48,557

Ivor R. Elrifi, Reg. No. 39,529
Attorney for Applicants
c/o Mintz, Levin
Telephone: (617) 542 6000
Fax: (617) 542 2241
Customer No. 30623

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